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Planning Brain Tumor Resection Using a Probabilistic Atlas of Cortical and Subcortical Structures Critical for Functional Processing: A Proof of Concept

BACKGROUND: Functional preoperative planning for resection of intrinsic brain tumors in eloquent areas is still a challenge. Predicting subcortical functional framework is especially difficult. Direct electrical stimulation (DES) is the recommended technique for resection of these lesions. A reliable probabilistic atlas of the critical cortical epicenters and subcortical framework based on DES data was recently published.

OBJECTIVE: To propose a pipeline for the automated alignment of the corticosubcortical maps of this atlas with T1-weighted MRI.

METHODS: To test the alignment, we selected 10 patients who underwent resection of brain lesions by using DES. We aligned different cortical and subcortical functional maps to preoperative volumetric T1 MRIs (with/without gadolinium). For each patient we quantified the quality of the alignment, and we calculated the match between the location of the functional sites found at DES and the functional maps of the atlas.

RESULTS: We found an accurate brain extraction and alignment of the functional maps with both the T1 MRIs of each patient. The matching analysis between functional maps and functional responses collected during surgeries was 88% at cortical and, importantly, 100% at subcortical level, providing a further proof of the correct alignment.

CONCLUSION: We demonstrated quantitatively and qualitatively the reliability of this tool that may be used for presurgical planning, providing further functional information at the cortical level and a unique probabilistic prevision of distribution of the critical subcortical structures. Finally, this tool offers the chance for multimodal planning through integrating this functional information with other neuroradiological and neurophysiological techniques.

KEY WORDS: Preoperative planning, Functional atlas, Direct electrical stimulation, Brain mapping, Neuro-oncology

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Surgical planning for intra-axial, infiltrating brain lesions is still a challenge for modern neurosurgery. Different noninvasive approaches have been proposed for the identification of functionally critical cortical and subcortical structures. Tractography,[1,2] functional MRI (fMRI, resting-state or task-based),[3,4] and/or transcranial magnetic stimulation (TMS)[5] have been used to characterize structural and functional brain networks, providing increasingly accurate results. Nevertheless, actually these data are not sufficient in establishing whether a specific structure is absolutely critical for a given function. As a consequence, these techniques cannot be fully "trusted" for neurosurgical planning, especially at the subcortical level.[3,6-9] Finally, no tools are currently available for mapping the subcortical functional framework.

ABBREVIATIONS: 3D, three-dimensional; **CI,** confidence interval; **DES,** direct electrical stimulation; **DSC,** dice similarity coefficient; **HGGs,** high-grade gliomas; **MNI,** Montreal Neurological Institute; **fMRI,** functional MRI; **MRI,** magnetic resonance imaging; **ROI,** region of interest; **TMS,** transcranial magnetic stimulation

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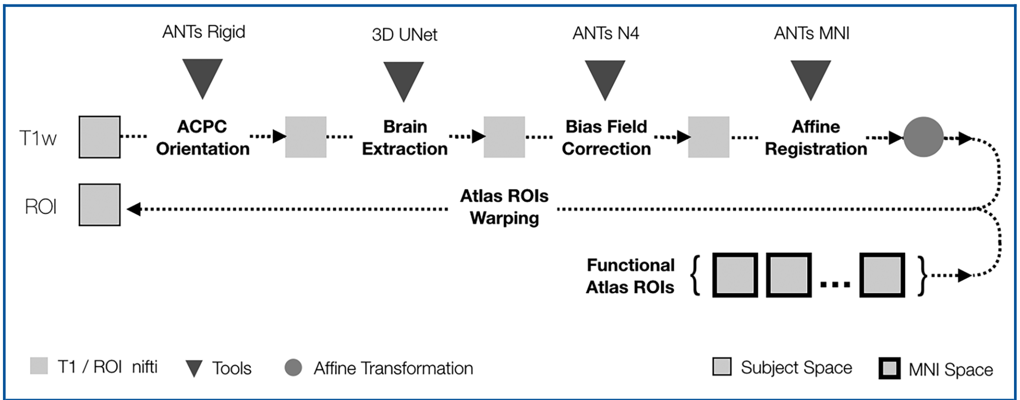

FIGURE 1. *Framework of the pipeline used for the alignment of MRI T1-weighted volumetric sequences with the niftii probabilistic maps of the corticosubcortical functional atlas. ANT, advanced normalization tool (ANTs toolkit, http://stnava.github.io/ANTs/); MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; ROI, region of interest.*

The widespread use of intraoperative direct electrical stimulation (DES) during awake surgery has improved the clinical and oncological outcome of patients with lesions involving eloquent areas (ie, gliomas, cavernous angioma)[10-12] and is also providing innovative neuroscientific insights into the complex anatomo-functional organization of the human brain connectome.[13,14] Moreover, data coming from DES has been used for computing cortical[15,16] and subcortical[17,18] atlases: recently, a large data set including 1821 cortical and subcortical DES functional responses in a series of 256 patients have been reported. These results were used to compute probabilistic maps specific for 16 key human brain functions (ie, semantic and phonological language elaboration; nonverbal comprehension; speech articulation and output; acoustic responses; reading; anomia; eye movements; language and motor planning; mentalizing; motor; motor control; somatosensory; spatial perception; visual) in a normalized Montreal Neurological Institute (MNI) space.[19,20] These data can be extremely useful for presurgical planning, especially for asleep surgery. Moreover, these maps have the unique value to predict the distribution of the subcortical functional framework for different neurological functions.

Here, we describe an automated pipeline to align the probabilistic maps of critical cortical and subcortical structures to an individual patient's magnetic resonance imaging (MRI) and we discuss possible applications of this tool for patient counseling and presurgical planning. This manuscript followed the STROBE guidelines.[21]

METHODS

Preoperative MRI Data

All patients underwent to a preoperative MRI (between 7 and 3 d before surgery), on a 1.5 T scanner (Clinical Optima MR450w, General Electrics) with an imaging protocol that included a 3-dimensional (3D) T1-weighted (T1-w) inversion recovery gradient echo sequence for structural imaging (axial acquisition, TR/TI/TE = 10.64/450/4.23 ms, FA = 12°, square FOV = 256 mm, voxel size = $1 \times 1 \times 1$ mm^3, ASSET acceleration factor = 2).

Alignment Tool

The tool consists of an initial preprocessing of the subject's T1-w images, followed by registration onto a template atlas (MNI-152, T1-1mm), to warp the labels of the functional atlas to the individual subject space (Figure 1).[22-25]

A full description of the tool is provided in **Supplemental Digital Content 1**.

Surgical Series and Technique

We selected 10 patients (7 males; mean age 47.5 yr; all right-handed at Edinburgh Handedness Inventory Test), who underwent asleep-awake-asleep surgery for resection of intrinsic brain lesions (5 low-grade gliomas, 4 high-grade gliomas, and 1 cavernous angioma) between May 2017 and February 2020 in the Neurosurgical Department of the first Author. Each patient underwent an accurate preoperative MRI planning, including T1-weighted volumetric sequences, with and without gadolinium, and volumetric T2/Flair, resting-state fMRI sequences, and diffusion weighted imaging (DWI) for tractography. The preoperative standard neurological examination and neurocognitive assessment (performed within 1 wk before the surgery and including

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TABLE 1. Summary of age, lesion site, histological diagnosis, and cortical and subcortical functional maps selected for each patients included in the series

	Age (yr)	Lesion site	Diagnosis	Cortical functional maps	Subcortical functional maps
Patient_1	41	Left parietal	Diffuse astrocytoma, grade II WHO	Semantic paraphasia, phonological paraphasia, visual, speech arrest, anomia, verbal apraxia	Semantic paraphasia, phonological paraphasia, visual, speech arrest, anomia, verbal apraxia
Patient_2	63	Right mid precentral	Anaplastic astrocytoma, grade III WHO	Motor, motor arrest, somatosensory, eyes movements, speech arrest, verbal apraxia	Motor, motor arrest, somatosensory, eyes movements, speech arrest, verbal apraxia
Patient_3	25	Left deep temporobasal	Diffuse astrocytoma, grade II WHO	Semantic paraphasia, phonological paraphasia, alexia, speech arrest, verbal apraxia, anomia	Semantic paraphasia, phonological paraphasia, alexia, verbal apraxia, anomia
Patient_4	52	Right posterior temporal	Anaplastic oligo-dendroglioma, grade III WHO	Visual, spatial perception, speech arrest, verbal apraxia, asemantism	Visual, spatial perception, speech arrest, verbal apraxia, asemantism
Patient_5	33	Left Wernicke's area	Gangliocytoma, grade I WHO	Semantic paraphasia, phonological paraphasia, alexia, speech arrest, verbal apraxia, anomia	Semantic paraphasia, phonological paraphasia, alexia, verbal apraxia, anomia
Patient_6	44	Left dorsal precentral	Diffuse astrocytoma, grade III WHO	Motor, motor arrest, somato-sensory, eyes movements, speech arrest	Motor, motor arrest, somato-sensory, eyes apraxia, speech arrest
Patient_7	74	Right dorsal precentral	Diffuse astrocytoma, grade II WHO	Motor, motor arrest, somatosensory, eyes movements, speech arrest	Motor, motor arrest, somatosensory, eyes apraxia, speech arrest
Patient_8	53	Left temporobasal	Cavernous angioma	Semantic paraphasia, phonological paraphasia, alexia, speech arrest, anomia	Semantic paraphasia, phonological paraphasia, alexia, anomia
Patient_9	53	Left precuneus	Diffuse astrocytoma, grade II WHO	Semantic paraphasia, phonological paraphasia, visual, speech arrest, verbal apraxia, anomia	Semantic paraphasia, phonological paraphasia, visual, speech arrest, verbal apraxia, anomia
Patient_10	37	Right temporal	Glioblastoma, grade IV WHO	Visual, spatial perception, speech arrest, verbal apraxia, asemantism	Visual, spatial perception, speech arrest, verbal apraxia, asemantism

memory, attention, language, and executive functions, as previously reported)[24,25] was normal in all patients. Patients with high-grade gliomas (HGGs) underwent to antiedema therapy with dexamethasone. Patients underwent corticosubcortical DES (5 mm bipolar stimulator, 60 Hz, 1 ms) mapping during neuropsychological monitoring (see **Supplemental Digital Content 2** for a full description).[3,4,16,17,19,26-30] The threshold for cortical and subcortical mapping (range: 1.75-4 mA) was set by eliciting speech arrest during a counting task at the level of the ventral premotor cortex (VPMC) in all cases, except patients 6, 7, and 9, where the intensity threshold was set by evoking an overt motor response after stimulation of the precentral gyrus. The full details of intra-operative testing and a description of DES and surgical technique are reported in the **Supplemental Digital Content 3**, **Text and 10 Figures**. All the neuroradiological and surgical procedures reported are routinely performed according to the approvals of the IRB.

This mix-series, including different brain lesions in both hemispheres (see Table 1) and exclusively resections performed with DES awake mapping, was selected in order to use the functional information (not belonging to the atlas dataset) for providing a qualitative evaluation of the functional maps alignment. For the ex-post quantitative and qualitative analysis of the alignment provided by this tool, in fact, specific cortical and subcortical maps were selected from the atlas for each case, on the basis of the topography of the different lesion (Table 1). Finally, we aligned the volumetric preoperative T1-w images to the selected functional cortical and subcortical probabilistic maps.[19,20]

Collection of Intraoperative Functional Responses

According to a previously validated method,[15-20] with a large reproducibility and validation reported in literature,[31-36] the volumetric T1-w MRI with gadolinium performed after surgery in all cases was spatially normalized to the T1 MNI 152 template (1 mm^3 of voxel spatial resolution). The intraoperative functional responses were manually collected by the first coauthor directly on the MNI-normalized T1 sequence of each patient, using a combination of regional cortical (eg, sulci, vessels, etc) and subcortical (eg, resection cavity, ventricular, etc) landmarks and confirming the final position with the coordinated reconstructions on axial, sagittal, and coronal planes, as previously reported. The MNI space coordinates (x, y, z) of each cortical and subcortical functional response was used for the subsequent analyses.

Analyses

To verify the reliability of our tool we calculated the accuracy error of brain mask extraction for subject's T1-w images with and without gadolinium for a good preprocessing and we measured the Dice similarity coefficient (DSC) for estimation of functional region of interests (ROIs) alignment and overlap with both images.

Finally, we verified the correspondence of intraoperative functional responses collected for every patient and their respectively functional-related ROIs, merged in their individual T1-w native space, as a measurement of alignment accuracy.

Ethics

The study followed the ethical standards of the Declaration of Helsinki. Patients gave their informed consent to the surgical procedure.

RESULTS

Alignment

The tool succeeded in accurate brain extraction with T1-w images in all cases, also using T1-w images with gadolinium. Considering the brain masks extracted from the T1-w sequence as reference, the accuracy error of brain mask extraction from T1-w images with gadolinium was lower than 7‰, for the same subject.

Registration of cortical and subcortical regions from the MNI-152-T1 (1 mm) template to volumetric T1-w (1 mm) was accurate (Figures 2A-2C and 3). Regarding registration accuracy, a rigid transformation was computed between paired T1-w and T1-w with gadolinium images for each subject, and then applied to the ROIs. For each pair of ROIs we measured the Dice coefficient, ie, a measure of the degree of 2 ROIs overlap, which is 1 when overlap is perfect. In our cases, the overlap degree is highly satisfactory, both for cortical and subcortical ROIs (DSC 0.92 and 0.94, respectively).

Regarding DES points, we considered ROIs from the functional atlas registered to T1-w with gadolinium space as reference, projecting the coordinates of stimulation points to this voxel space, and we computed whether these points fell in their respective functionally-related ROIs with an approximation of 10 mm (considering the 5 mm spacing of the bipolar stimulator), as previously reported.[3,4,19]

The mean coherence between the stimulation points and the functional ROIs was 93.7%, considering functions (Table 2), and 93.1%, considering subjects (Table 3).

Intraoperative Brain Mapping Comparison

From intraoperative cortical and subcortical DES, we collected 57 functional responses: motor 17 (11 cortical); somato-sensory 10 (8 cortical); speech arrest 9 (all cortical); verbal apraxia 3 (all subcortical); anomia 9 (7 cortical); semantic paraphasia 1 (subcortical); and visual 8 (all subcortical). A full description is provided in the **Supplemental Digital Content 3**, **Text and 10 Figures**. Figures 2 and 3 show the preoperative planning provided by the alignment of cortical and subcortical functional maps, the postoperative MRI, the intraoperative pictures of the cartography of functional sites at the cortical and the subcortical levels, and a visual comparison of the coregistered functional maps, with respect to the intraoperative mapping pictures and postoperative MRI. We found a complete matching (100%), at both cortical and subcortical level, between DES and probabilistic maps of motor, somato-sensory, visual, verbal apraxia, anomia, semantic paraphasia, and speech arrest networks in Cases 2, 3, 4, 5, 6, 7, 8, 10. Exclusively 2 functional responses in Case 1, and 2 functional responses in Case 9 (anomia for both patients) were more than 10 mm out of the of the probabilistic functional maps coregistered (Figure 3).

DISCUSSION

When approaching intrinsic brain lesions, the main goal should be maximizing the extent of resection, while reducing postoperative—especially permanent—deficits. As a consequence, identification of cortical functional epicenters and the critical subcortical connectivity is still a challenge in modern neurosurgery. Despite its growing use for surgical planning, functional neuroimaging has limitations in distinguishing the structures essential for neural functions that must be preserved during surgery from those that may be compensable after resection. Moreover, no imaging or neurophysiological techniques are available for identification of white matter functional framework. For these reasons, currently the most reliable tool allowing for precise identification of cortical and subcortical eloquent structures at the individual level is DES during neurocognitive monitoring in awake conditions.[10]

Here, we propose an innovative tool allowing a fully automated alignment of MRI sequences with functional cortical and subcortical maps from a large DES dataset, including 16 networks.[19,20] For a reliable test of the accuracy of brain extraction and ROIs alignment, we performed quantitative and qualitative analysis on the T1-weighted (with and without gadolinium) MRI in a cohort of 10 patients, who underwent resection of different brain lesions located in eloquent areas, using awake corticosubcortical DES mapping and not belonging to the original series utilized for the atlas computation. We voluntary included a heterogenous group of patients, to verify the reliability of this tool. The pipeline was set up to align probabilistic atlas data onto the T1-w images of an individual patient.

We demonstrated maximum rate of success (100%) in brain extraction after uploading individual patient preoperative T1-w scans in all patients, with an accuracy error of brain mask extraction from T1-w images with gadolinium lower than 7‰. However, we suggest using the preoperative T1 without

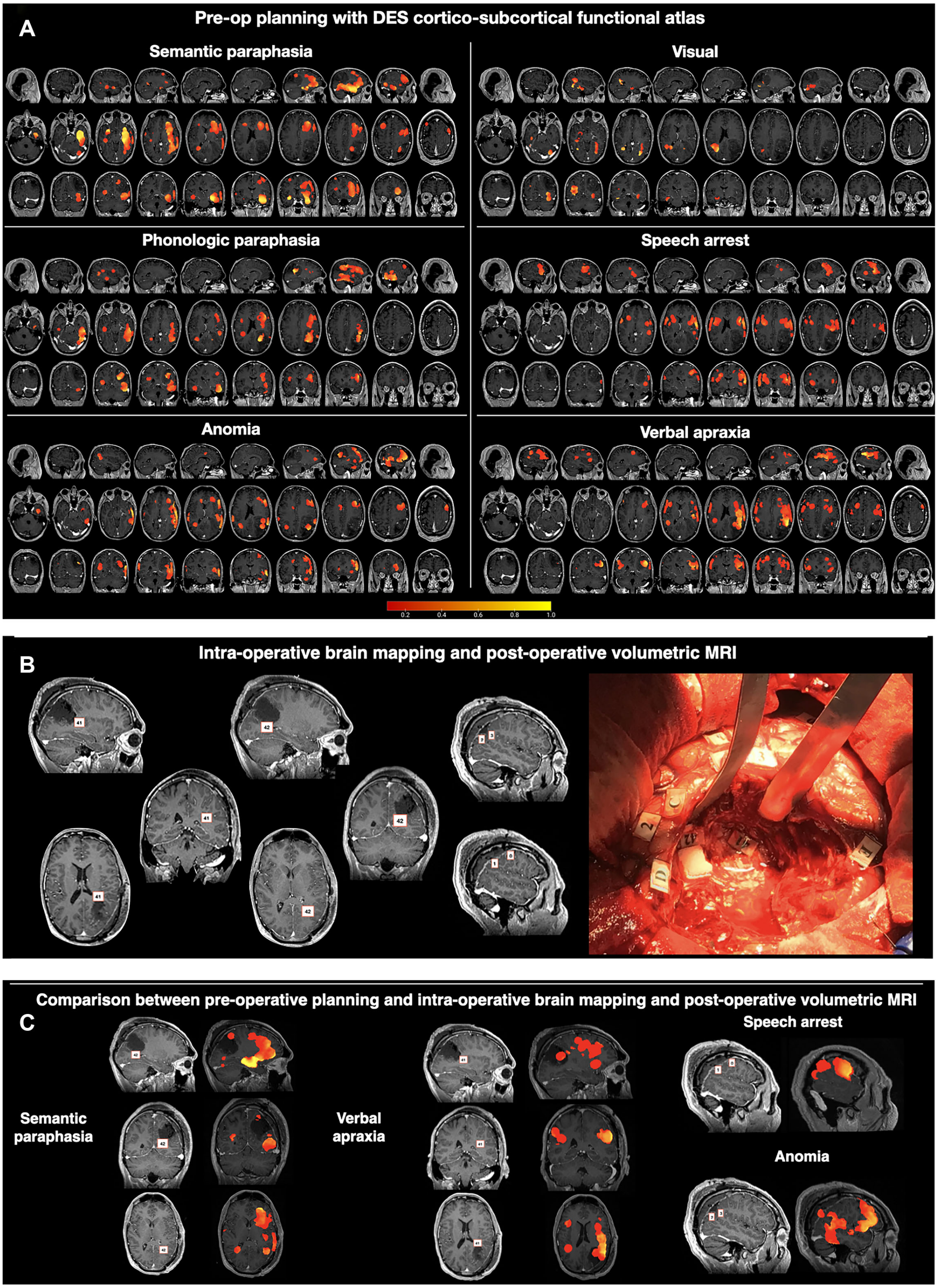

FIGURE 2. **A**, *Results of automated alignment of the preoperative volumetric T1-weighted sequence with the functional cortical and subcortical maps selected for this case.* **B**, *Results of the intraoperative DES mapping with neuropsychological monitoring and correlation with the postoperative T1-weighted sequence.* **C**, *Comparison between preoperative corticosubcortical functional planning and results of intraoperative functional DES mapping.*

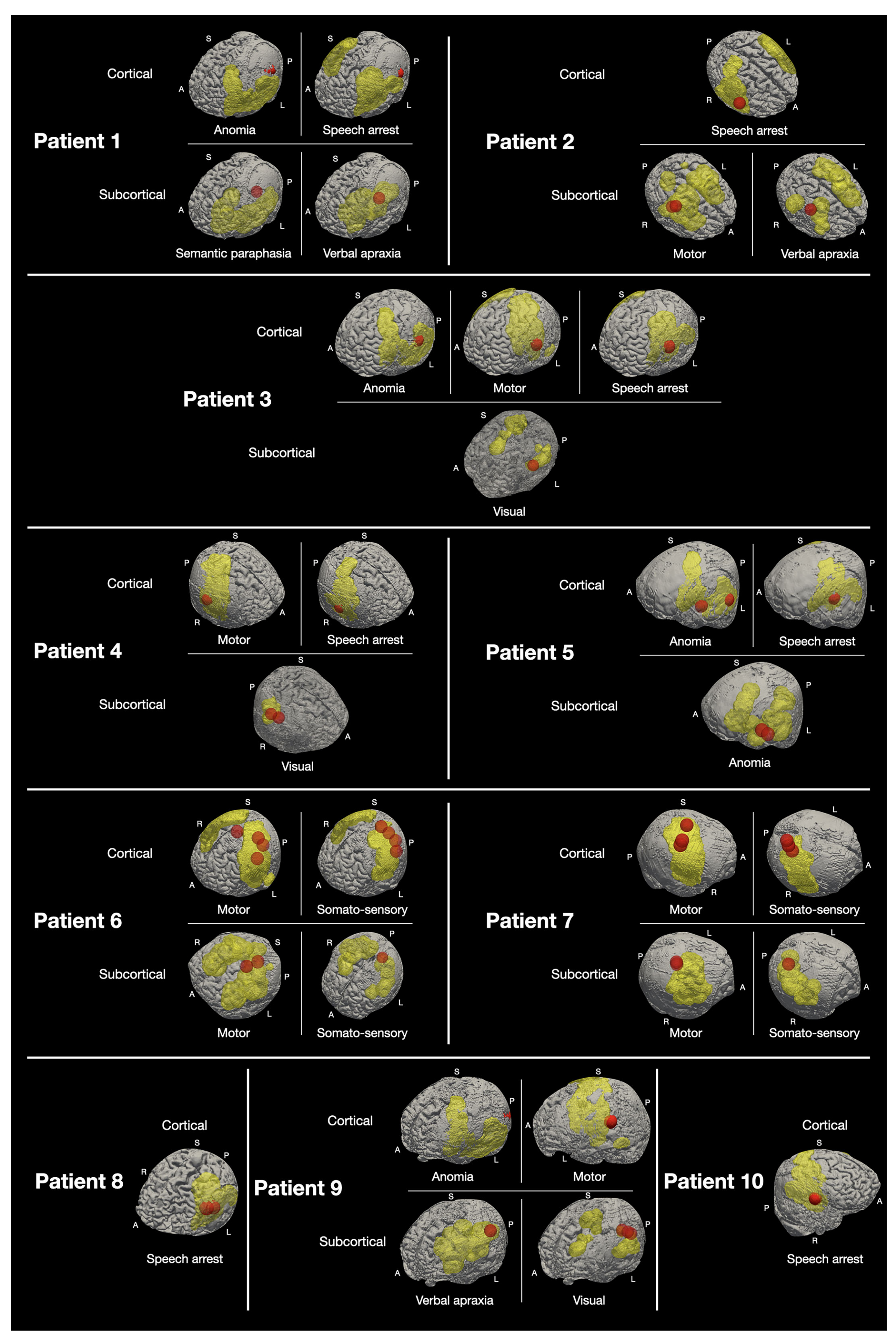
Patient 1
Cortical
Anomia
Speech arrest
Subcortical
Semantic paraphasia
Verbal apraxia
Patient 2
Cortical
Speech arrest
Subcortical
Motor
Verbal apraxia
Patient 3
Cortical
Anomia
Motor
Speech arrest
Subcortical
Visual
Patient 4
Cortical
Motor
Speech arrest
Subcortical
Visual
Patient 5
Cortical
Anomia
Speech arrest
Subcortical
Anomia
Patient 6
Cortical
Motor
Somato-sensory
Subcortical
Motor
Somato-sensory
Patient 7
Cortical
Motor
Somato-sensory
Subcortical
Motor
Somato-sensory
Patient 8
Cortical
Speech arrest
Patient 9
Cortical
Anomia
Motor
Subcortical
Verbal apraxia
Visual
Patient 10
Cortical
Speech arrest

FIGURE 3. *Summary of brain-extracted 3D models of all the patients selected in this series, including the anatomic location of all functional responses collected during surgery at the cortical and subcortical level (represented as 10 mm-diameter sphere), and the overlap with the respective cortical and subcortical functional maps.*

TABLE 2. Percentage of inclusion of the stimulation points in the functional ROIs with 10 mm tolerance

Functional response	Cortical	Subcortical	Total
Anomia	43%	100%	56%
Motor	100%	100%	100%
Semantic paraphasia	–	100%	100%
Sensorial	100%	100%	100%
Speech arrest	100%	–	100%
Verbal apraxia	–	100%	100%
Visual	–	100%	100%
Total	88%	100%	98%

TABLE 3. Percentage of inclusion of the stimulation points within the functional ROIs in the different subjects (10 mm tolerance)

Patient	Cortical	Subcortical	Total
1	33%	100%	60%
2	100%	100%	100%
3	100%	100%	100%
4	100%	100%	100%
5	100%	100%	100%
6	100%	100%	100%
7	100%	100%	100%
8	100%	–	100%
9	33%	100%	71%
10	100%	100%	100%

gadolinium as input file, as the tool produces separate niftii files for each functional map requested that can be opened on other sequences of the same patient (eg, T1-w with gadolinium and/or T2/FLAIR), or uploaded into neuronavigation. Finally, the second quantitative parameter (DSC) for evaluating the alignment of the ROIs of the different functional maps showed good results at both the cortical and subcortical level (DSC 0.92 and 0.94, respectively).

For the qualitative estimation of the alignment, we calculated the match of the functional responses found during DES in this series in respect to the functional cortical and subcortical maps selected for each case. In all cases but 2, we demonstrated an accurate matching between functional responses evoked at the individual level and the coregistered probabilistic group-level components from DES atlas (88% and 100% at the cortical and subcortical levels, respectively). One possible explanation for the discrepancy in Cases 2 and 9 is the larger size of the surgical cavities compared to the others (see **Supplemental Digital Content 3, Text and 10 Figures**). In fact, the slow discordance involved the cortical level, where the intraoperative deformation was highest. Given that affine transformation may not be suitable for the management of high local tissue distortion, we suggest considering nonlinear transformations with higher degree of freedom, to improve the quality of alignment when approaching large surgical cavities. Nevertheless, these results are quite favorable in comparison also to other noninvasive and established techniques for preoperative functional planning (eg, fMRI, TMS).[3,37]

We believe that this tool may have many important implications for neurosurgical and clinical uses. In particular: (1) evaluating the expected extent of resection and counseling patients on the surgical risk profile expected; (2) for asleep surgery, providing unique information regarding the subcortical functional connectivity not available with other preoperative techniques; (3) for awake surgery, selecting the most appropriate paradigm for intraoperative testing; (4) identifying the most critical regions for planning intraoperative mapping; (5) improving individual neurosurgeon's knowledge of the complex 3D anatomofunctional structure of brain networks.

Finally, the role of this functional information may be particularly useful in a multimodal setting, for integrating these data with other neuroradiological (ie, tractography and fMRI) and even neurophysiological (eg, TMS) techniques with the final goal of a further improvement of the preoperative planning and of neuroscientific knowledge of the human brain.

Limitations and Future Developments

Despite the number of functional responses collected (57), the small series of cases included for the quantitative and qualitative evaluation of the functional maps alignment is a limitation of this paper, and larger and various dataset are needed for a more complete evaluation of this tool. The results are currently limited to a relatively simple affine registration of the MNI template, with the motivation of minimizing the requirements for taking advantage of the DES functional atlas, and making the tool of practical use to most neurosurgeons.

Moreover, a more accurate registration might be obtained by applying diffeomorphic transformation. Nevertheless, additional inputs would be provided, eg, mask of tumor and gray/white matter tissue segmentation.

Finally, we used for this tool the functional maps with the full range of probability and the CI (in color scale) reported in the atlas,[19] thus visualizing functional maps with a larger distribution. The probability threshold could be in future adjustable allowing the clinicians to customize the information provided by these maps.

CONCLUSION

In this proof of concept, we developed a simple and reliable pipeline, allowing for an automated linear registration of a patient's volumetric T1 MRI sequences with functional information based on a previously validated probabilistic atlas.

The tool requires a standard T1-weighted MRI as input, and output separate niftii files containing critical cortical and subcortical data concerning 16 functional domains. Our preliminary results demonstrated a high reliability of brain extraction and alignment of the functional maps to the T1 MRI of the patients. The matching analysis between the positive DES sites at individual level in this series and the maps of the functional atlas had a significant high mean level of coherence for different neurological functions.

This tool, available online at http://nilab.fbk.eu/services, might be of special interest for the neurosurgical community. In fact, this is a complementary technique for preoperative planning with the unique value to provide information regarding the subcortical functional framework, allowing also an integrated use with other neuroradiological and neurophysiological techniques. Further implementation of the tool will contribute in validating the method for different pathologies (eg, vascular, epilepsy surgery), and in extending possible application to more challenging aspects of intraoperative mapping.

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Supplemental Digital Content 3. Text and 10 Figures. A full description and discussion of the entire surgical series included in this manuscript as legends of 10 Figures, showing the full report (imaging and intraoperative pictures) of each case.